way to analyze our data would have been to pool all the data obtained with the two different LMWHs; major chemical, biological and clinical differences exist between these LMWHs, and there has been much debate on this issue. We believe that pooling these data would have generated many more letters to the editor!

There are few biological markers of prognosis in unstable angina. Our recent studies have focused attention on vWf as a new marker of potential interest in acute coronary syndromes. It appeared consistently as a predictive factor of outcome, and we believe it deserves attention and further evaluation in large studies. Our most recent publication demonstrated that the new anticoagulants tested in unstable angina behave better than UH with regards to vWf release. We agree it should also be confirmed. Step-by-step we are progressing in the understanding of the role of vWf in the prognosis of unstable angina, and the time has come for head-to-head comparisons between the new anticoagulant treatments. In that regard, the ARMADA study has now been completed and we will share the data very soon. I am sure that Dr. Hödl will appreciate the results.

Gilles Montalescot, MD
Department of Cardiology
Centre Hospitalier
Universitaire Pitie-Salpetriere
47 Boulevard de l'Hopital
75013 Paris France
E-mail: gilles.montalescot@psl.ap-hop-paris.fr

PII S0735-1097(01)01259-1

REFERENCES

1. Montalescot G, Collet JP, Lison L, et al. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. J Am Coll Cardiol 2000;36:110–4.
2. Montalescot G, Philippe F, Ankri A, et al. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. Circulation 1998;98:287–9.
3. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation 1997;96:61–8.

Enoxaparin for Acute Coronary Syndromes?

Goodman et al. (1) conclude that enoxaparin is a more effective antithrombotic treatment than unfractionated heparin (UFH) for the prevention of rebound ischemia in patients with unstable angina or non-Q-wave myocardial infarction. We suggest an alternative conclusion.

Enoxaparin's plasma half-life is two to four times longer as compared to UFH after subcutaneous administration (2), even more when compared to UFH given intravenously, as in the Goodman et al. study. Activity against factor Xa and thrombin disappears only after more than 16 h (3), following moderate doses of enoxaparin. With high doses, as used in the ESSENCE study (1), enoxaparin's plasma half-life is substantially longer (4).

Therefore, after stopping study drugs in the ESSENCE study, enoxaparin's antithrombotic effect very likely lasted much longer than that of UFH. After stopping UFH, ischemic events during the 48-h monitoring period were twice as frequent as after stopping enoxaparin (45% vs. 26%), whereas there was no difference while on active treatment (25%)—compatible with an antithrombotic effect lasting about one day longer after enoxaparin. In addition, enoxaparin's antithrombotic effect wanes much more slowly as compared to IV UFH. This may have added benefit by attenuating a heparin rebound effect.

It remains to be convincingly shown whether enoxaparin or other low-molecular-weight heparins exert superior antithrombotic effects as compared to UFH. Superior clinical benefit might be explained by pharmacokinetic differences only. For patients with acute coronary syndromes, extending the duration and slower weaning (5) of IV UFH may well be better and cheaper.

Christoph Pechlaner, MD
Innsbruck University Hospital
Medical Intensive Care Unit
Anichstr. 35
A-6020 Innsbruck
Austria
E-mail: christoph.pechlaner@uibk.ac.at

Walter Gritsch, MD
Christian Wiedermann, MD

PII S0735-1097(01)01260-8

REFERENCES

1. Goodman SG, Barr A, Sobtchouk A, et al. Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST Segment Monitoring Substudy. J Am Coll Cardiol 2000;36:1507–13.
2. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997;337:688–98.
3. Agnelli G, Iorio A, Renga C, et al. Prolonged antithrombin activity of low-molecular-weight heparins. Clinical implications for the treatment of thromboembolic diseases. Circulation 1995;92:2819–24.
4. Dawes J. Comparison of the pharmacokinetics of enoxaparin (Clexane) and unfractionated heparin. Acta Chir Scand 1990;556 Suppl:68–74.
5. Becker RC, Spencer FA, Li Y, et al. Thrombin generation after the abrupt cessation of intravenous unfractionated heparin among patients with acute coronary syndromes: potential mechanisms for heightened prothrombotic potential. J Am Coll Cardiol 1999;34:1020–7.

REPLY

Pechlaner et al. suggest that our findings (1) of less rebound ischemia with enoxaparin as compared to unfractionated heparin (UFH) are simply due to the longer half-life of enoxaparin. However, the ischemic episodes (average number and duration) identified during continuous electrocardiographic monitoring were statistically significantly lower in the enoxaparin as compared to the UFH group not only during the first 12 h after drug discontinuation but also during the >12 to 24-h and even the >36 to 48-h time intervals. This suggests that the benefit seen with enoxaparin is not simply due to prolonged half-life and greater anti-Xa:IIa activity that "wanes" more slowly than UFH. Indeed, there is growing evidence supporting additional mechanisms of benefit of enoxaparin over UFH beyond the differences in pharmacokinetics; for example, the significant blunting of the rise of von Willebrand factor with enoxaparin in the first 48 h of treatment (2).

As we noted, our substudy (1) was stopped at the time of overall trial completion but prior to enrollment of an adequately powered sample size to confidently address the initial 48-h period of active

treatment. Nonetheless, among the subgroup of patients who underwent monitoring during both the initial treatment and study drug discontinuation periods (n = 163), ischemia was less frequently observed during *both* monitoring periods in the enoxaparin group (18.4% vs. 32.2%, p = 0.045 and 25% vs. 46%, p = 0.005, respectively). Further, the time to first ischemic episode was significantly earlier among UFH-treated patients, consistent with a superior *early* antithrombotic effect of enoxaparin and a reduction in the composite clinical end point of death, myocardial infarction (MI), and need for urgent revascularization (3).

Therefore, we believe that enoxaparin has been shown to be superior to UFH based upon the consistent and statistically significant reductions in the composite and double (death/MI) end points in ESSENCE and TIMI 11B (4). In contrast, "extending the duration and slower weaning" of UFH is an unproven method of administration, and, in fact, the cost-savings realized with enoxaparin ultimately make it the *less* expensive option (5).

Shaun G. Goodman, MD, FACC
Anatoly Langer, MD, FACC
Division of Cardiology
St. Michael's Hospital
30 Bond Street
Room 9-005 Queen
Toronto, ON M5B 1W8, Canada
E-mail: goodmans@smh.toronto.on.ca

PII S0735-1097(01)01261-X

REFERENCES

1. Goodman SG, Barr A, Sobtchouk A, et al. Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST Segment Monitoring Substudy. J Am Coll Cardiol 2000;36:1507–13.
2. Montalescot G, Collet JP, Lison L, et al. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. J Am Coll Cardiol 2000;36:110–4.
3. Lopez-Sendon J, Antman EM, McCabe CH, et al. Superiority of enoxaparin over unfractionated heparin in unstable angina occurs early in treatment: results from TIMI 11B (abstr). J Am Coll Cardiol 1999;33:352A.
4. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B–ESSENCE meta-analysis. Circulation 1999;100:1602–8.
5. O'Brien BJ, Willan A, Blackhouse G, Goeree R, Cohen M, Goodman S. Is the use of low-molecular-weight heparin (enoxaparin) in acute coronary syndrome patients cost saving in Canada? Am Heart J 2000;139:423–9.

Failure of Right Ventricular Recovery of Fallot Patients After Pulmonary Valve Replacement: Delay of Reoperation or Surgical Technique?

We read with great interest and surprise the article published by Therrien et al. in the November issue of the *Journal* (1). These results are extremely disappointing. All the physicians familiar with the treatment of patients with repaired tetralogy of Fallot share the idea that one should not wait too long before implanting a valve in the right ventricular outflow tract of patients presenting with dilated right ventricle. Extremely dilated right ventricles might not benefit from valvulation as much as moderately dilated ones. However, it is extremely surprising that all patients operated on in a major center like Toronto showed neither clinical improvement nor regression of ventricular volumes after reoperation.

Although their patients were operated on quite late, we wonder whether their unexpectedly bad results might not be related to another reason than the delay for reoperation. The Toronto team has the peculiarity of implanting bioprosthetic material in the right ventricular outflow tract of these patients. Almost all patients received a stented bioprosthesis varying in size between 25 and 33 mm in diameter. It is noteworthy that true diameters of the outer rings are even larger than these measurements. The only way to implant these rather bulky bioprostheses at the level of the pulmonary annulus is to cover them with a patch extending from the main pulmonary artery to the infundibulum of the right ventricle. The immediate effect of this patching is to further increase the size of the right ventricular cavity, which may at least partly explain the fact that no decrease was observed in end-systolic and end-diastolic volumes of these patients after reoperation. We have recently shown that pulmonary insufficiency might not be the leading factor causing right ventricular dilation after repair of tetralogy of Fallot, and we suspect that the contractile function of the pulmonary infundibulum may play a role in the preservation of right ventricular function (2). Adding a patch to this already weakened area might further contribute to the deterioration of this function.

Like others, we believe that homografts are the ideal valve substitute for the right ventricular outflow tract because they offer a better effective orifice area, and they do not necessitate a patch enlargement. Although 40% of the patients presented in this series had an aneurysm resection, it is not clear whether the researchers believe that they effectively reduced right ventricular size at the time of the procedure.

In conclusion, we wonder whether the extremely poor results presented by Therrien et al. (1) might not be at least partially explained by their surgical technique rather than by the delay in the reoperation. The insertion of a patch in the already dilated area of the pulmonary infundibulum might further impede right ventricular function and as such increase rather than decrease right ventricular volumes.

Yves d'Udekem, MD
Cliniques Universitaires Saint-Luc
Avenue Hippocrate 10
B-1200 Brussels
Belgium
E-mail: dudekem@chir.ucl.ac.be

Jean Rubay, PhD
Caroline Ovaert, MD

PII S0735-1097(01)01256-6

REFERENCES

1. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? J Am Coll Cardiol 2000;36:1670–5.